

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 2

Amendments to the claims:

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1. (currently amended) A method of detecting whether a subject is either predisposed to or afflicted with a pulmonary disease hypertension which comprises (1) obtaining a suitable sample from the subject; and (2) detecting in the sample a bone morphogenetic protein receptor-II mutation which is not present in a suitable sample of wildtype bone morphogenetic protein receptor-II,

wherein the presence of a mutation indicates that the subject is predisposed to or afflicted with the pulmonary disease hypertension.

2. (currently amended) The method of claim 1, wherein the suitable sample ~~is a~~ comprises nucleic acid sample, and the mutation is detected in a nucleic acid molecule encoding bone morphogenetic protein receptor-II.

3. (currently amended) The method of claim 1, wherein the suitable sample ~~is one which~~ comprises a bone morphogenetic protein receptor-II polypeptide, and the mutation is detected in the bone morphogenetic protein receptor-II polypeptide.

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 3

4. (currently amended) The method of claim 1, wherein the pulmonary disease hypertension is Primary Pulmonary Hypertension.
5. (original) The method of claim 4, wherein the Primary Pulmonary Hypertension is Familial Primary Pulmonary Hypertension.
6. (previously canceled)
7. (canceled)
8. (canceled)
9. (previously canceled)
10. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a nucleotide segment guanosine-guanosine-guanosine-guanosine-adenosine located at positions 1099-1103 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
11. (original) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a glutamic acid

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 4

residue located at position 368 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.

12. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a thymidine residue located at position 2579 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq SEQ ID NO:1.
13. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at an asparagine residue located at position 861 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.
14. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a replacement of a nucleotide segment cytosine-thymidine-thymidine-thymidine located at positions 507-510 in a wildtype nucleic acid with a nucleotide segment adenosine-adenosine-adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
15. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of a cysteine located at position 169 in a

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 5

wildtype polypeptide to a termination codon, which wildtype polypeptide comprises the sequence set forth in SEQ ID NO:2.

16. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a cytosine located at position number 2617 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
17. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position 873 in a wiltype polypeptide to a termination codon, which wildtype polypeptide comprises the sequence set forth in SEQ ID NO:2.
18. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a replacement of a nucleotide segment adenosine-guanosine present at positions 690-691 in a wildtype nucleic acid with a thymidine residue, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
19. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a lysine residue located at position 230 in a wildtype polypeptide, which wildtype

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 6

polypeptide comprises the sequence set forth in SEQ ID NO:2.

20. (previously canceled)

21. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a cytosine located at position number 1471 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

22. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a mutation of an arginine located at position 491 in a wildtype polypeptide to a tryptophan, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

23. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a guanosine located at position number 1472 in a wildtype nucleic acid to an adenine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

24. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of an arginine located at position number 491 in a wildtype

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 7

polypeptide to a glutamine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

25. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a nucleotide segment adenosine-thymidine-thymidine-thymidine located at positions 1248-1251 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
26. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of an phenylalanine located at position number 417 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
27. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a cytosine located at position number 994 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
28. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of an arginine located at position number 332 in a wildtype polypeptide to a

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 8

stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.

29. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a thymidine located at position number 295 in a wildtype nucleic acid to a cytosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
30. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of a cysteine located at position number 99 in a wildtype polypeptide to an arginine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
31. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a guanosine residue located at position 1097 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq SEQ ID NO:1.
32. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a proline residue located at position 366 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 9

33. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a guanosine located at position number 727 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
34. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of a glutamic acid located at position number 243 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
35. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of an adenosine residue located at position 1214 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in Seq SEQ ID NO:1.
36. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at an aspartic acid residue located at position 405 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.
37. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 10

nucleotide segment adenosine-cytosine located at positions 2441-2442 in a wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

38. The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide comprises a frameshift mutation at a histidine residue located at position 814 in the wildtype polypeptide, which wildtype polypeptide comprises the amino acid sequence set forth in SEQ ID NO:2.
39. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a cytosine located at position number 2695 in a wildtype nucleic acid to a thymidine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
40. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II ~~polypeptide~~ polypeptide comprises a mutation of an arginine located at position number 899 in a wildtype polypeptide to a stop codon, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
41. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a deletion of a nucleotide segment present at positions 189-209 in a

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 11

wildtype nucleic acid, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

42. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a deletion of an amino acid segment serine-threonine-cysteine-tyrosine-glycine-leucine-tryptophan located at position numbers 64-70 in a wildtype polypeptide, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
43. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a guanosine located at position number 296 in a wildtype nucleic acid to a adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
44. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of a cysteine located at position number 99 in a wildtype polypeptide to a tyrosine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
45. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a thymidine located at position number 250 in a wildtype

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 12

nucleic acid to a cytosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.

46. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of a cysteine located at position number 84 in a wildtype polypeptide to an arginine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
47. (currently amended) The method of claim 2, wherein the mutated nucleic acid molecule comprises a mutation of a guanosine located at position number 1040 in a wildtype nucleic acid to a adenosine, which wildtype nucleic acid comprises the sequence set forth in SEQ ID NO:1.
48. (currently amended) The method of claim 3, wherein the mutated bone morphogenetic protein receptor-II polypeptide polypeptide comprises a mutation of a cysteine located at position number 347 in a wildtype polypeptide to a tyrosine, which wildtype polypeptide has the sequence set forth in SEQ ID NO:2.
49. The method of claim 5, wherein the subject is suffering from an asthmatic symptom, so as to thereby prevent a subject afflicted with Familial Primary Pulmonary Hypertension from being misdiagnosed as asthmatic.

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 13

50. (previously canceled)

51. (currently amended) A method of predicting an increased likelihood of a subject giving birth to twins or triplets which comprises:

- a) obtaining a suitable nucleic acid sample from the subject;
- b) detecting the presence of one copy of a mutant nucleic acid molecule which encodes a bone morphogenetic protein receptor-II polypeptide, thereby indicating that the subject is heterozygous for the mutation,

wherein heterozygosity predicts an increased likelihood of the subject giving birth to twins or triplets.

52. (currently amended) A method of predicting an increased likelihood of a subject having a miscarriage prior to giving birth to a child which comprises:

- a) obtaining a suitable nucleic acid sample from the subject;
- b) detecting the presence of two copies of a mutant nucleic acid molecule which encodes a bone morphogenetic protein receptor-II polypeptide, thereby indicating that the subject is homozygous for the mutation,

wherein homozygosity predicts an increased likelihood of the subject having a miscarriage prior to giving birth to a child.

Applicants: Jane H. Morse and James A. Knowles
Serial No.: 09/904,380
Filed : July 12, 2001
Page 14

53. (withdrawn)

54. (previously canceled)

55. (withdrawn)

56. (allowed) A method of detecting whether a subject is either predisposed to or afflicted with Familial Primary Pulmonary Hypertension which comprises:

- a) obtaining a suitable nucleic acid sample from the subject; and
- b) detecting the presence of a (GGC)₁₂ trinucleotide repeat at positions -928 to -963 in the 5' end of the bone morphogenetic protein receptor-II gene,

wherein the presence of the trinucleotide repeat indicates that the subject is either predisposed to or afflicted with Familial Primary Pulmonary Hypertension.

57. (withdrawn)

58. (previously canceled)

59-60. (withdrawn)

61-63. (previously canceled)